REMARKS

I. Introduction

Claims 1-3 and 11-26 are pending in this application. Claims 24-26 have been withdrawn by the Examiner as being drawn to a non-elected invention. Claims 4-10 have been cancelled according to a Preliminary Amendment filed on March 21, 2005.

II. Rejection Under 35 U.S.C. § 112, First Paragraph: Enablement

Claims 1-3 and 11-23 stand rejected under 35 U.S.C. § 112, first paragraph. The rejection states that "the specification, while being enabled for treating arthritis and ulcerative colitis, does not reasonably provide enablement for treating any autoimmune disorder." August 27, 2007 Office Action, pg. 4. Specifically, the rejection notes that this is a highly unpredictable art, the findings are highly unlikely, the specification provides limited guidance, and there is a lack of a working example.

An applicant's specification is presumptively enabled for the full scope of the claims. *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); *accord*, M.P.E.P. § 2164.04. In fact, "[a]s a matter of Patent Office practice...[a specification] must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements." *In re Ambruster*, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975).

The test of enablement is whether one of ordinary skill in the art could make the invention from the disclosure in the patent coupled with information known in the art without undue experimentation. M.P.E.P. § 2164.01. To determine whether experimentation is undue, the Examiner must apply the eight factors identified in the Federal Circuit's decision in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). M.P.E.P. § 2164.01(a).

The M.P.E.P. specifically states that the Examiner has the initial burden to establish a reasonable basis to question the enablement of the claimed invention. M.P.E.P. § 2164.04. This reasonable basis may be established by the Examiner by "making specific findings of fact, supported by evidence, and then drawing conclusions based on these findings of fact...[h]owever, specific technical reasons are always required." *Id.* Absent such evidence, the burden does not shift to the Applicants. *In re Marzocchi*, 169 U.S.P.Q. at 369.

In the present case, the rejection does not include sufficient evidence of a lack of enablement. Instead, it merely includes a general discussion of the aforementioned *Wands* factors which provide broad rationales and support for the current rejections. Accordingly, until sufficient evidence has been provided showing that one skilled in the art would need more information to practice the full scope of the invention, a *prima facie* case of lack of enablement has not been established. M.P.E.P. § 2164.04.

Applicants have provided a generic teaching of the method of treating an autoimmune disorder using certain compounds, provided a range of suitable dosages, listed a variety of autoimmune disorders which the method could be used to treat, disclosed the structure of the compounds to be used in the method, provided a manner of producing certain of these compounds, and provided examples of treating a subject suffering from several of the enumerated autoimmune disorders, namely arthritis and ulcerative colitis. One skilled in the art, following this teaching, could apply well-known principles of biological diagnostic and treatment techniques to practice the claimed method as broadly as claimed. Applicants note that, under the law, the scope of enablement is more than what is disclosed in the specification but also includes the scope of what would be known to one of ordinary skill in the art. *National Recovery Technologies Inc. v. Magnetic Separation Systems Inc.*, 49 U.S.P.Q.2d 1671, 1676 (Fed. Cir. 1999). Moreover, the Examiner has acknowledged that artisans in the field of the invention possess an extremely high level of skill. August 27, 2007 Office Action, pg. 5.

In the Office Action, it is also asserted that "the lack of a working example to treat any autoimmune disorder, is a critical factor to be considered." August 27, 2007 Office Action, pg. 7. Applicants are surprised by such an unsupported assertion. Applicants specifically provided working examples on pages 48-53 that are enabling for methods of treating an autoimmune disorder, specifically arthritis and ulcerative colitis. Furthermore, pages 8-9 of the present specification provide examples of other autoimmune disorders which the claimed method could be used to treat. Clearly, Applicants need not provide the results of detailed experiments showing the use of the claimed method to treat a subject suffering from each and every disorder classified as an autoimmune disorder for the claim to be enabled. Surely one skilled in the art, especially when such a person possesses an extremely high level of skill, could apply the method disclosed throughout the application, including the working examples, to a subject suffering from

an autoimmune disorder, such as those listed on pages 8-9, without resorting to undue experimentation. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d at 1404.

Unquestionably, one of ordinary skill in the art could follow the teachings of the specification and the included examples to make and use the invention claimed in claims 1-3 and 11-23. Given the details of the specification and examples, one of ordinary skill in the art would have more than sufficient information to perform the method claimed on a subject suffering from any autoimmune disorder without having to resort to undue experimentation. The present specification provides a large amount of direction by the inventors, as well as numerous examples. Accordingly, a proper analysis of the *Wands* factors necessarily leads to the conclusion that the present specification shows how to make and use the claimed invention without undue experimentation, and Applicants respectfully request withdrawal of this rejection under § 112, first paragraph.

III. Rejection Under 35 U.S.C. § 103(a)

Claims 1-3 and 11-23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yang et al. (U.S. Pub. No. 2002/0049222) as evidenced by van Heek et al. (British Journal of Pharmacology, 2001, Vol. 134, pp. 409-417) in view of Somers (U.S. Pat. No. 6,147,250).

The present application is directed to a method of treating autoimmune disorders by administering to a patient suffering from such a disorder an effective amount of a sterol absorption inhibitor. In another embodiment, the present application is directed to a method of treating a patient suffering from an autoimmune disorder by administering, in addition to the sterol absorption inhibitor previously mentioned, a HMG CoA reductase inhibitor. The formation of lipid rafts within the cell membranes of leukocytes play a critical role in T-cell and B-cell activation, antigen presentation, adhesion molecule function, and chemokine receptor signaling, each of which is associated with the pathogenesis of autoimmune disorders. Because both cholesterol and plant sterols are essential to the structure of these rafts, and thus the downstream autoimmune pathogenesis, Applicants have discovered that reducing the intestinal

disruption of cholesterol and/or plant sterols can provide an effective method of treating or preventing autoimmune diseases by disrupting the formation of these lipid rafts.

Yang teaches a method of treating conditions associated with inflammation, including arthritis and multiple sclerosis, by administering modulators of chemokine receptor activity. According to Yang, activation of the chemokine receptor CCR-2 by chemo-attractant protein-1 (MCP-1) plays a major role in monocyte recruitment to inflammatory sites, and opposition of this activity will sufficiently suppress the immune response to produce therapeutic benefits in immuno-inflammatory and autoimmune diseases. Yang, at ¶ 0006. Thus, Yang's invention is directed to compounds that, acting alone, can treat conditions associated with inflammation by modulating chemokine receptors such as the CCR-2 receptor. Yang, at ¶ 0007-0009. The compounds taught by Yang to accomplish this have at least two asymmetric centers at the 1- and 3-positions of the cyclopentyl ring and are of the general formula shown as Formula I in paragraphs [0010] through [0114].

Applicants, on the other hand, have discovered that certain sterol absorption inhibitors can, acting alone, treat and prevent autoimmune disorders by disrupting the formation of lipid rafts within the leukocytes. The compounds of Yang are structurally dissimilar to the compounds of Formulae I-IX used in the claimed methods of the present invention. The compounds recited by Applicants in Formulae I-IX are sterol absorption inhibitors, which do not inhibit activation of CCR-2 receptors, and Yang fails to disclose or suggest that such compounds could be used instead of CCR-2 modulators to treat a patient suffering from an autoimmune disorder.

Yang also discloses that his CCR-2 modulators can be co-administered with various other active ingredients which are not CCR-2 modulators, such as cholesterol absorption inhibitors like ezetimibe. Yang, at ¶ 0371. However, there is no indication in Yang that these other compounds are capable of treating or preventing an autoimmune disorder. The inclusion of such cholesterol absorption inhibitors in Yang is for other, more conventional uses of these compounds. At the time Yang filed his application it was unknown that ezetimibe could be used for treating or preventing autoimmune disorders. Thus, absent any indication to the contrary, co-administering ezetimibe with the CCR-2 receptor modulator in Yang was clearly intended to lower plasma cholesterol rather than to treat the autoimmune disorder itself. If in fact Yang had known of the

propensity of sterol absorption inhibitors to treat autoimmune disorders, there would be no need to co-administer it with the primary compound taught in Yang. Further, there is no indication in any of the cited art that such a sterol absorption inhibitor would be successful in treating an autoimmune disorder. It is a principal of patent law that, in making a rejection for obviousness under 35 U.S.C. § 103(a) there must be at least a reasonable expectation of success in modifying the cited art references. *See In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); M.P.E.P. § 2143.02.

This deficiency of Yang is not cured by the disclosure of Van Heek or Somers. Van Heek is not directed to the treatment of autoimmune disorders at all but is instead concerned with the effect of ezetimibe in the treatment of atherosclerosis. Somers is directed to HMG-CoA reductase inhibitor compounds that are allegedly useful in lowering LDL levels and selectively inhibiting the expression of vascular cell adhesion molecule-1 (VCAM-1). According to Somers, HMG-CoA reductase inhibitors inhibit adhesion molecule functions in leukocytes. Somers is not directed to, nor does it disclose, the use of sterol absorption inhibitors, such as ezetimibe, or the use of these compounds in the treatment of autoimmune disorders.

Applicants have discovered that disrupting lipid raft formation in the plasma membrane of leukocytes will prevent the leukocyte trafficking which causes autoimmune disorders. The relationship between lipid raft formation and autoimmune disorders was not disclosed in Yang, which is focused instead on the relationship between the CCR-2 chemokine receptors and certain disorders, or Somers, which is directed to the relationship between cardiovascular disorders and the expression of VCAM-1. Further, the ability of sterol absorption inhibitors to treat autoimmune disorders or affect adhesion molecule function was also unknown. The cited art gives no reasonable expectation of Applicants' success since, as previously mentioned, the cited art is instead focused on the treatment of autoimmune disorders by mediating other biochemical pathways, namely the CCR-2 and VCAM-1 receptors. Consequently, one skilled in the art would not find it obvious in light of the cited art to administer a sterol absorption inhibitor, such as ezetimibe, to a patient to treat an autoimmune disorder.

IV. Conclusion

For all of the foregoing reasons, Applicants submit that pending claims 1-3 and 11-26 comply with the requirements of 35 U.S.C. § 112, are patentable over the cited references, and are in condition for allowance. Accordingly, reconsideration of the rejections and allowance of pending claims 1-3 and 11-26 are respectfully requested.

Should the Examiner have any questions regarding any of the foregoing or wish to discuss this application in further detail to advance prosecution, the Examiner is invited to contact Applicants' undersigned representative at the telephone number provided below.

Respectfully submitted,

By _____

Bryan P. Clark
Registration No. 60,465
Attorney for Applicants
700 Koppers Building
436 Seventh Avenue
Pittsburgh, PA 15219
Telephone: 412-471-8815
Facsimile: 412-471-4094
E-mail: webblaw@webblaw.com